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2000.09.04 2000-021670(+2000GB-021670) *(2002.03.14)* C07D 211/46, A61K 31/445, C07D 401/12

New piperidine derivatives are modulators of chemokine receptor activity, useful for treating, e.g. asthma, rhinitis or autoimmune, inflammatory, proliferative or immunological diseases (Eng)

C2002-102505 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW)

Addnl. Data: SANGANEE H, SPRINGTHORPE B
2001.08.30 2001WO-SE01869

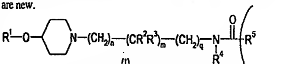
B(6-B1, 6-D1, 6-D2, 6-D3, 6-D7, 6-D9, 7-D5, 14-A1, 14-A2B1, 14-C1, 14-C3, 14-C6, 14-C9, 14-E8, 14-F7, 14-F9, 14-G2, 14-G2A, 14-H1, 14-J1A4, 14-J1B3, 14-K1A, 14-K1B, 14-N3, 14-N14, 14-N17C, 14-S4) .17

NOVELTY

New piperidine derivatives (I) active as modulators of chemokine receptor activity are useful for treating e.g. asthma or rhinitis or autoimmune, inflammatory, proliferative or immunological diseases.

DETAILED DESCRIPTION

Piperidine derivatives of formula (I) and their salts and solvates are new.



(I)

R^1 = phenyl (optionally substituted by cyano, $S(O)_2$(1-6C alkyl), $S(O)_2$(1-6C haloalkyl), halo, 1-6C alkyl, 1-6C haloalkyl or 1-6C alkoxy);
n = 0-4;
m = 0 or 1; when m is 0 then q is 0, and when m is 1 then q is 1, 2 or 3;
when R^2 and R^3 H or 1-6C alkyl, and R^4 = H, then R^5 = a 3-10-

reactant: $R_5 - \overset{O}{\overset{\|}{C}} - L$ →

membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms selected from N, O and S, the ring system being substituted at least once with 1-6C alkyl (substituted with NH_2, CO_2(1-6C alkyl), $S(O)_2$(1-6C alkyl), $NHS(O)_2$(1-6C alkyl) or $S(O)_2NR^{13}R^{14}$), $S(O)_2$(1-6C alkyl), $S(O)_2$(1-6C hydroxyalkyl), $S(O)_2NH$(1-6C alkyl), NHC(O)(1-6C alkyl), $NHS(O)_2$(1-6C alkyl), 1-6C alkoxy (substituted with 1-6C alkoxy, OH, CO_2(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH_2), 2-6C alkenyl, pyrrolyl and δ^3-pyrrolinyl; and optionally further substituted with halo, cyano, nitro, OH, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkoxycarbonyl, 1-6C haloalkyl, 1-6C haloalkoxy, NR^6R^7, 3-6C cycloalkylamino, 1-6C alkylthio, 1-6C alkythio(1-6C alkyl), 1-6C alkylcarbonylamino, $C(O)NR^8R^9$, sulfonamido ($S(O)_2NH_2$), (di)1-6C alkylsulfonamido, phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl and $C(O)R^{10}$- substituted 1-6C alkyl or 1-6C alkoxy;
when R^2 and R^3 H or 1-6C alkyl and R^4 = 1-4C alkyl or 3-6C cycloalkyl(1-4C alkyl), then R^5 = a 3-10-membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatnms selected from N, O and S, the ring system being optionally substituted by halo, cyano, nitro, OH, 1-6C alkyl (optionally substituted with halo, 1-6C alkylthio, NH_2, $C(O)R^{10}$, CO_2(1-6C alkyl), $S(O)_2$(1-6C alkyl), $NHS(O)_2$(1-6C alkyl) or $S(O)_2NR^{13}R^{14}$), 3-6C cycloalkyl, 1-6C alkoxy (substituted with halo, 1-6C alkoxy, OH, $C(O)R^{10}$, CO_2(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH_2), 2-6C alkenyl, 1-6C alkoxycarbonyl, NR^6R^7, 3-6C cycloalkylamino, 1-6C alkylthio, 1-6C alkylcarbonylamino, $C(O)NR^8R^9$, sulfonamido ($S(O)_2NH_2$), (di)1-6C alkylsulfonamido, $S(O)_2$(1-6C alkyl), $S(O)_2$(1-6C hydroxyalkyl), $S(O)_2NH$(1-6C alkyl), NHC(O)(1-6C alkyl), $NHS(O)_2$(1-6C alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or δ^3-pyrrolinyl; and
when R^2 = phenyl (optionally substituted with halo, 1-4C alkyl or 1-4C alkoxy), R^3 = H or 1-6C alkyl, and R^4 = H, 1-4C alkyl or 3-6C cycloalkyl(1-4C alkyl), then R^5 a 3-10-membered saturated or unsaturated ring system which may comprise up to 2 ring C atoms that form carbonyl groups and which may comprise up to 4 ring heteroatoms selected from N, O and S, the ring system being optionally substituted by halo, cyano, nitro, OH, 1-6C alkyl (optionally substituted with halo, 1-6C alkylthio, NH_2, $C(O)R^{10}$, CO_2(1-6C alkyl), $S(O)_2$(1-6C alkyl). $NHS(O)_2$(1-6C alkyl) or

$S(O)_2NR^{13}R^{14}$), 3-6C cycloalkyl, 1-6C alkoxy (substituted with halogen, 1-6C alkoxy, OH, $C(O)R^{10}$, CO_2(1-6C alkyl), NHC(O)O(1-6C alkyl) or NH_2), 2-6C alkenyl, 1-6C alkoxycarbonyl, NR^6R^7, 3-6C cycloalkylamino, 1-6C alkylthio 1-6C alkylcarbonylamino, $C(O)NR^8R^9$, sulfonamido ($S(O)_2NH_2$), (di)1-6C alkylsulfonamido, $S(O)_2$(1-6C alkyl), $S(O)_2$(1-6C hydroxyalkyl), $S(O)_2NH$(1-6C alkyl), NHC(O)(1-6C alkyl), $NHS(O)_2$(1-6C alkyl), phenyl, phenylamino, nitrophenyl, pyridyl, pyridylthio, benzodioxanyl, thienyl, furanyl, pyrrolyl or δ^3-pyrrolinyl;
R^{10} = OH or $NR^{11}R^{12}$; and
R^6-R^9 and R^{11}-R^{14} = H or 1-6C alkyl;
provided that n+m+q = 1, 2, 3 or 4.
INDEPENDENT CLAIMS are also included for:
(1) the preparation of (I); and
(2) use of (I) in the manufacture of a medicament.

ACTIVITY

Antiasthmatic; Antiallergic; Antiinflammatory; Immunosuppressive; Cytostatic; Anti-HIV; Virucide; Antitussive; Antiarthritic; Antirheumatic; Opthalmological; Antipsoriatic; Dermatological; Antiulcer; Antimigraine; Analgesic; Neuroprotective; Nootropic; Antiarteriosclerotic; Thyromimetic; Antidiabetic; Nephrotropic; Antileprotic; Antibacterial; Hemostatic; Gynecological.

MECHANISM OF ACTION

Modulators of chemokine receptor (especially CCR3) activity; H1 antagonists.
Test details are described but no results are given.

USE

The compounds can be used to treat a CCR3 mediated disease state e.g. asthma or rhinitis (claimed). They can be used to treat asthma (e.g. allergic or dust asthma), or rhinitis (e.g. acute or chronic rhinitis, e.g. rhinitis caseosa, membranous rhinitis including croupous or vasomotor rhinitis). They can also be used for treating e.g. autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and AIDS). The compounds are also H1 antagonists and may be used in the treatment of allergic disorders.

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They can be used to treat respiratory tract obstructive disease of airways e.g. chronic obstructive pulmonary disease (COPD), bronchitis, sarcoidosis, farmer's lung and related diseases, nasal polyposis, fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough; (bone and joints) arthrides e.g. rheumatic, infectious, autoimmune, spondyloarthropathies (e.g. ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis; (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermitides, seborrhoeic dermatitis, Lichen planus, pemphigus, bullous pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata or vernal conjunctivitis; (gastrointestinal tract) Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (e.g. migraine, rhinitis or eczema)'; allograft rejection, acute and chronic following e.g. transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea, or chronic graft versus host disease; and/or other tissues or diseases such as Alzheimer's disease, multiple sclerosis, atherosclerosis, AIDS, lupus disorders (such as systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fasciitis, hyper IgE syndrome, leprosy (e.g. lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

ADMINISTRATION

(I) can be used in doses of e.g. 0.01-100, (preferably 0.1-20) mg/kg/ay by e.g. oral, parenteral or topical routes.

EXAMPLE

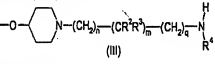
2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethylamine (0.20 g) was dissolved in dichloromethane (4 ml). 3-[(Methylsulfonyl)methyl]benzoic acid (see WO00/15609; or by hydrolysis of methyl 3-[(methylsulfonyl)methyl]benzoate, 0.132 g) triethylamine (0.289 ml) and PyBrop (RTM, 0.483 g) were added. After 24 hours at room temperature sodium hydrogen carbonate (aqueous) was added and the product extracted with diethyl ether. The organics were dried and concentrated. Purification by reverse phase high pressure liquid chromatography (with a gradient eluent system (25% acetonitrile/NH_4OAc (aqueous, 0.1%) to 95% acetonitrile/NH_4OAc (aqueous, 0.1%) (any excess NH_4OAc was

2002-362237/39

removed by dissolving the compound in dichloromethane and washing with aqueous saturated sodium hydrogen carbonate followed by drying of the organics with magnesium sulfate and evaporation of solvent) gave N-[2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]ethyl]-3-[(methylsulfonyl)methyl]benzamide (0.101 g, m. pt. 112-114 °C).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) may be prepared by reacting a piperidine compound of formula (III) with a compound of formula $LC(=O)R^3$ (IV), (claimed).



(III)

L = a leaving group.

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